

of the women diagnosed with ovarian cancer will die prematurely as a result. Little is known of the causes of ovarian cancer; epidemiologic studies suggest that menstrual, environmental, and genetic factors are important. Evidence for the role of environmental factors is primarily population based and suggest that dietary factors and chemical carcinogens are contributors to increased risk. The intramural and extramural NIEHS expertise in the areas of chemical carcinogenesis and growth factor biology, along with ongoing research projects in the area of genetic predisposition to ovarian cancer, provide the foundation for an expanded and productive research agenda in this area.

Endometrial carcinoma is the most frequently diagnosed gynecologic malignancy in the United States, but remains the least studied of the major cancers affecting women. Unlike cancers of the breast and ovary, endometrial cancer is limited primarily to women over the age of 50, and well-established risk factors suggest probable etiologic factors, most relating to estrogen. Researchers at NIEHS have used molecular genetic approaches to distinguish etiologic factors and animal models (including transgenic mice) to understand the role of physiologic and environmental factors in endometrial carcinogenesis.

Diethylstilbestrol as a Model for Environmental Estrogens

The health effects of diethylstilbestrol (DES) exposure are a research priority that reflects the convergence of several related investigative projects that are major areas of concern for NIEHS. The synthetic estrogen DES was administered to pregnant women during the 1940s through 1960s, originally for high-risk pregnancies but later to promote "healthier babies" as well. Subsequently, the drug was linked to the development of an otherwise extremely rare malignancy, clear-cell carcinoma of the vagina, in young female offspring exposed *in utero*. In addition, a number of more common non-neoplastic changes in the reproductive tract of DES-exposed daughters were identified, including vaginal adenosis, cervical ectropion, and numerous other structural abnormalities. Although the public health hazards associated with further exposure to DES have been largely eliminated, there are a number of compelling reasons for the continued study of DES-exposed women, as well as for basic research on the biological effects of DES and other environmental estrogenic compounds.

First, it is unclear whether the human cancer incidence resulting from DES exposure has peaked. Although the majority of DES daughters have passed the age range

for vaginal carcinoma development, few have reached the age range (postmenopausal) in which endometrial carcinoma typically occurs in the DES unexposed population, and endometrial carcinoma occurs with a much higher prevalence than vaginal carcinoma in DES-treated mice. Similarly, the threat of breast cancer is still a concern in this population. The identification of molecular genetic markers for DES carcinogenicity is therefore a continuing priority; such markers would also be of value in predicting risk for third-generation DES offspring, for whom little is known about potential health risks.

Second, DES may be viewed as a model compound for other environmental agents with estrogenic potential. The bioaccumulation of these environmental estrogens is recognized as a problem of increasing magnitude, and certain human populations in the United States have been shown to carry amounts of these fat-soluble compounds which, in fish and other wildlife, cause significant endocrine dysfunction and developmental anomalies of the reproductive tract. Insights into the biological effects of DES should therefore provide a foundation upon which future environmental health problems may be effectively addressed.

NIEHS has a long history of accomplishments in conducting and supporting research on estrogen action, hormonal carcinogenesis, and other types of estrogen-related pathology, particularly for DES and similar compounds. More recent achievements have provided insights into basic mechanisms of estrogen receptor action at the molecular level. A transgenic mouse that overexpresses the estrogen receptor is being developed to study tissue susceptibility and mechanisms for hormonal carcinogenesis. New endeavors include the analysis of human and animal tumors resulting from DES exposure *in utero* for molecular genetic alterations. Rapid advances in the fields of molecular and developmental biology have provided numerous insights into relevant genes and molecular pathways involved in reproductive tract development. Epidemiologic studies are focused on a broad range of health effects among DES-exposed men and women. Expanded research efforts are necessary to use this knowledge in exploring the epigenetic effects of DES in relation to reproductive tract malformations at the molecular level.

In addition to the estrogen receptor, research on the role of "orphan receptors" in environmental disease is promising. Identification and characterization of orphan receptors and their endogenous ligands will provide a link to understanding the molecular mechanisms through which

exogenous chemicals may exert toxic effects and through which natural substances influence physiologic processes. For example, a recently discovered member of the nuclear receptor family apparently recognizes a class of foreign chemicals called peroxisome proliferators, which includes industrial plasticizers, herbicides, and hypolipidemic agents. Similarly, a receptor from another gene family exists for the ubiquitous xenobiotic dioxin, or TCDD. A related example is the retinoids, which regulate differentiation and growth of a variety of epithelial tissues including mammary gland, cervical, vaginal, and uterine epithelium. Ongoing research at NIEHS is directed toward understanding the process of squamous differentiation in gynecologic epithelial tissues by retinoids and estrogens, and interactions between the retinoic acid receptor and estrogen receptor signaling pathways. Further research is necessary to define these pathways at the molecular level and to elucidate possible therapeutic applications of retinoids in breast and other cancers.

Role of the Environment in Osteoporosis

Osteoporosis is a complex disorder of the skeletal system characterized by decreased bone mass, which leads to increased skeletal fragility and fracturing. The pathogenesis of this metabolic disorder is likely to be multifactorial, involving genetic, racial, and environmental factors including smoking, diet, and alcohol. Interactions between the endocrine and immune systems appear to play a key role in maintaining the physiological homeostasis in bone metabolism. Exposure to estrogenic substances, a number of which are widespread in the environment, can influence bone pathology, as can exposure to heavy metals. Researchers at NIEHS are using cell culture and animal studies to investigate the molecular mechanisms of estrogen receptor-mediated effects on bone development and metabolism, and NIEHS-supported studies are investigating the role of metals such as aluminum and cadmium in osteodystrophies. Important questions remain regarding the competition of these metals with calcium in bone deposition and reabsorption. Because the condition appears to be more severe in women without ovarian activity (e.g., postmenopausal), understanding the modulatory effects of estrogens on heavy-metal toxicity may contribute to our knowledge of the process of osteoporosis.

We now know, that early exposure to DES at very low doses can affect bone density. Basic and clinical studies are now focusing on the potential role that dose and time of exposure to estrogenic sub-

stances may have on changes in bone density. These findings could play a significant role in the development of early intervention strategies for women with osteoporosis. In addition, clinical trials are beginning at NIEHS to determine if pathologic conditions that modify endogenous estrogen levels and disrupt a normal pubertal period (such as precocious puberty or Turner syndrome) might also influence bone density at later stages of life. The health and monetary costs of osteoporosis to our society are already enormous, estimated at \$7–10 billion annually and affecting approximately 24 million Americans, the majority of whom are women. An estimated 50% of women over age 45 and 90% of women over age 75 have osteoporosis. As the average age of our society increases, the number of people afflicted with this disease will rise, resulting in increased health care costs. Expanded research in this area will extend our understanding from basic research studies to clinical investigations and affected human populations.

NIEHS to Play Unique Role in Women's Health Research Effort

Human disease is largely the product of the interaction between two factors, genetics and the environment, throughout the life span. Any large-scale research agenda pertaining to human health must therefore consider the entire life span, and it is clear that women's health is worse over the course of a life time than men's. It is equally apparent that the environmental component of this interaction has been somewhat neglected by the biomedical research community. A major research initiative addressing the environment and women's health is therefore imperative. The proposed initiative thus focuses on hormonal carcinogenesis and endocrine toxicology, with special emphasis on the genetic and epigenetic molecular mechanisms that underlie these phenomena.

With NIEHS's background, knowledge, and ongoing research programs in women's health and insofar as a wide range of environmental agents possess hormonal potential and a significant percentage of women's health problems appear related to dysfunction in hormonal pathways, this approach is likely to succeed. Inclusion of the NIEHS extramural (grants) component in the above areas will undoubtedly facilitate research progress. The diverse strengths of extramurally funded research programs allow for important health problems with an environmental component, such as cardiovascular disease, to be addressed. Such a dual effort of the NIEHS intramural and extramural research programs will allow a comprehen-

sive, multidisciplinary, and inclusive approach to this problem.

Contributing to this report on women's health were Jeff Boyd, Laboratory of Molecular Carcinogenesis; J. Carl Barrett, Environmental Carcinogenesis Program; Terri Damstra, Program Coordination; and John McLachlan, Office of the Director.

Minority Health Research

Treatment of lead toxicity, environmental justice, and environmental health sciences centers are among the minority health issues that will be addressed through an agreement between the National Institutes of Health's Office of Research on Minority Health (ORMH), and NIEHS. A memorandum of agreement between the two NIH organizations provides NIEHS with \$5 million a year through 1997 to address minority health concerns related to environmental health.

John Ruffin, director of ORMH, and Kenneth Olden, director of NIEHS, signed the agreement March 29 at NIEHS in Research Triangle Park, North Carolina. The ORMH was established in 1990 to strengthen the efforts of NIH to improve the health status of minority Americans through biomedical research and to increase the participation of minorities in biomedical research.

Funds provided through the agreement will be apportioned between research programs relating to minority health and planning and research on issues of environmental justice. Environmental justice addresses pollution and environmental health risks and their distribution across socioeconomic

ic classes and racial groups. Four major efforts under the agreement are:

- Blood levels in children. Three to four million children in the United States have elevated blood lead levels. There are two possible interventions to reduce the problem. One is to reduce exposure including lead abatement in homes, but this will require years to accomplish. A more immediate approach is to treat children with a drug (chelating agent) that will remove lead from the body. Succimer is a new drug that holds promise but has not been adequately tested clinically for this purpose; it is the first newly approved drug of its type (chelating agent) since 1950. NIEHS will support a clinical trial to establish the effectiveness of succimer. It is orally administered, appears to be relatively safe, and does not cause as much loss of necessary elements such as zinc and iron as other chelators. Contracts to conduct the trials will be awarded in the next several months.
- Lead in pregnant women. Research will be conducted to learn to what extent the release of lead stored in bone is increased during pregnancy. This is an important question in understanding how the developing fetus may be exposed through lead exposure of the mother before pregnancy. The research will focus on women from Eastern Europe who were heavily exposed to lead who have and then migrated to Australia. This population provides a unique opportunity for this kind of study because of the recognizable differences in the nature of the lead iso-



Focus on minority health. John Ruffin (left), director of the Office of Research on Minority Health, and Kenneth Olden, director of NIEHS, sign a five-year agreement.